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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/590,896	08/28/2006	Toshihiro Ushijima	USHIJIMA3	5702

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EXAMINER	
OGUNBIYI, OLUWATOSIN A	

ART UNIT	PAPER NUMBER
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/590,896	USHIJIMA ET AL.	
	Examiner	Art Unit	
	OLUWATOSIN OGUNBIYI	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 September 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,14-17 and 23-45* is/are pending in the application.

4a) Of the above claim(s) *1-7 and 26-45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8,14-17 and 23-25* is/are rejected.

7)☒ Claim(s) *15 and 24* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *APPENDIX A*.

RESPONSE TO AMENDMENT

1. The amendment filed 9/30/09 has been entered into the record. Claims 9-13 and 18-22 have been cancelled. Claims 1-8, 14-17 and 23-45 are pending. Claims 1-7 and 26-45 are withdrawn. Claims 8, 14-17 and 23-25 are under examination.

Election/Restrictions

2. This application contains claim 1-7 and 26-45 drawn to an invention nonelected with traverse in the reply filed on 4/22/09. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Objections/Rejections Withdrawn

3. The objection to claims 11, 12, 13, 14, 15, 16 and 20-25 under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend on another multiple dependent claim is withdrawn in view of the amendment to the claims.

4. The objection of claims 8 and 17 for grammatical error is withdrawn in view of the amendment to the claims.

5. The rejection of claims 8-10 and 17-19 under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter is withdrawn in view of the amendment to the claims.

6. The rejection of claims 9-10 and 18-19 under 35 U.S.C. 112, second paragraph is withdrawn in view of the cancellation of the claims.

7. The rejection of claims 8-9 and 17-18 under 35 U.S.C. 102(b) as being anticipated by Imada et al. Journal of Clinical Microbiology, Nov. 2003, p. 5015-5021, cited in IDS is withdrawn in view of the amendment to the claims.

8. The rejection of claims 8-10 and 17-19 under 35 U.S.C. 102(b) as being anticipated by Makino et al. Microbial Pathogenesis 1998; 25:101-109 is withdrawn in view of the amendment to the claims.

New Objections/Rejections Based on Amendment

Claim Objections

9. Claims 15 and 24 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claims 15 and 24 recites that the "isolated variant has the sequence as depicted in SEQ ID NO: 2 with a deletion at the C-terminal wherein an amino acid substitution is introduced". However, claims 8 and 17 from which claims 15 and 24 depend respectively, teach that the isolated variant comprises particular amino acid substitutions at particular positions. Therefore, the recitation in claims 15 and 24 "a deletion at the C-terminal wherein an amino acid substitution is introduced" does not further limit claim 15 and 24.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 8, 14-17 and 23-25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a written description rejection.**

Independent claims 8 and 17 and dependent claims are drawn to:

an isolated variant of an *Erysipelothrix rhusiopathiae* surface protective antigen

or

a ΔSpaA protein, which is a shortened form of the SpaA protein in which a portion of the SpaA protein is deleted, which is immunogenic, and expressed in *E. coli* as inclusion bodies and has an amino acid sequence with an amino acid substitution consisting of one or a combination of more than one selected from the group consisting of (1) to (7) as described below:

(1) the 69th amino acid from the N-terminal
encompassing the signal sequence is substituted with glycine;

(2) the 154th amino acid from the N-terminal
encompassing the signal sequence is substituted with glycine;

(3) the 203rd amino acid from the N-terminal
encompassing the signal sequence is substituted with threonine;

(4) the 214th amino acid from the N-terminal
encompassing the signal sequence Is substituted with glutamine;

(5) the 253rd amino acid from the N-terminal
encompassing the signal sequence is substituted with threonine;

(6) the 278th amino acid from the N-terminal
encompassing the signal sequence ±s substituted with glycine;
and

(7) the 531st amino acid from the N-terminal
encompassing the signal sequence is substituted with glycine.

Claim 15 is drawn to the isolated variant of claim 8 or 14 which has an amino acid sequence as depicted in SEQ ID NO: 2 or the sequence as depicted in SEQ ID NO: 2 with a deletion at the C-terminal wherein an amino acid substitution is introduced.

Claim 24 is drawn to the composition of claim 17 or 23, wherein said isolated variant has an amino acid sequence as depicted in SEQ ID NO: 2 or the sequence as depicted in SEQ ID NO: 2 with a deletion at the C-terminal wherein an amino acid substitution is introduced.

The claims are drawn to a genus of proteins in which any portion of the SpaA protein is deleted and which is immunogenic and also comprising the recited amino acid substitution. The genus is highly variant comprising species of differing structure because any number of amino acid(s) at any location of the SpaA protein can be deleted. The scope of claims 15 and 24 are further drawn to a genus of proteins comprising fragments of SEQ ID NO: 2 (i.e. an amino acid sequence as depicted in SEQ ID NO: 2) up to the full sequence or variants of SEQ ID NO: 2.The claims require that the genus has to be immunogenic.

The specification teaches a ΔSpaA protein encoded by a partial SpaA gene up till the 1260th nucleotide and codes for a shortened form of SpaA protein (with deletion of 207 amino acid residues at the C-terminal) with particular amino acid substitutions at

particular positions, was found to be immunogenic. See p. 22 first incomplete paragraph and p. 41 from lines 7-25 and page 42-43.

The specification does not describe other deletion variants of a SpaA protein wherein the deletion variant further comprises the instant amino acid substitution(s) that is immunogenic.

The specification does not describe the common structure i.e. immunoepitope(s) of the genus of deletion variants of SpaA proteins further comprising the instant amino acid substitution(s) that correlates with function i.e. immunogenicity so that one of skill in the art can envision which amino acids or combinations of amino acids can be deleted in a Spa A protein in which the remaining SpaA protein further comprises the instant amino acid substitution(s) and still retain immunogenicity.

Antibody epitopes are characterized by the art as either continuous or discontinuous (see pages 23-25, 27-33, Harlow et al , Antibodies A Laboratory Manual, Cold Spring Harbor Laboratory Press Inc., 1988). T cell epitopes are continuous peptide fragments of a polypeptide or antigen that have been processed by an accessory cell. The art recognizes that defining epitopes is not easy and there is a confusing divergence between the textbook definition of epitope and the definition that is in use in published descriptions of experimental investigations and that epitopes must be empirically determined (Greenspan et al, Nature Biotechnology 17:936-937, 1999). The specification clearly lacks description of any particular antibody epitope (i.e. antigenic determinant), either continuous or discontinuous that is within a *E. rhusiopathie* SpaA protein.

Applicants clearly did not provide written description of any particular antibody-binding or T-cell binding epitope contained in the *E. rhusiopathie* SpaA and as such it is not clear which residue(s) can be deleted and still result in a deletion variant SpaA protein further comprising the instant amino acid substitution(s) and still possess immunogenicity.

Colman et al. (Research in Immunology 145: 33-36, 1994, p.33 column 2, p. 35

column 1) disclose that a single amino acid changes in an antigen can effectively abolish the interaction with an antibody. This underlies the importance of the description of the immunoepitope(s) and which amino acid deletion(s) and where and coupled with the instant amino acid substitutions in the deletion variant still retains immunogenicity. Houghten et al. (New Approaches to Immunization, Vaccines 86, Cold Spring Harbor Laboratory, p. 21-25, 1986) taught the criticality of individual amino acid residues and their positions in peptide antigen-antibody interactions. Houghten et al state (see page 24): "One could expect point mutations in the protein antigen to cause varying degrees of loss of protection, depending on the relative importance of the binding interaction of the altered residue. A protein having multiple antigenic sites, multiple point mutations, or accumulated point mutations at key residues could create a new antigen that is precipitously or progressively unrecognizable by any of the antibodies in the polyclonal pool."

The disclosure of only one member of the genus to which the claims are drawn is insufficient to describe the large and variant genus of proteins the scope of which is set forth above. In such an unpredictable art of protein mutation and the effect on antigenicity or immunogenicity as set forth supra, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus. See *Noelle v Lederman*. 355 F. 3d 1343, 1350, 69 USPQ2d 1508, 1514 (*Fed. Cir. 2004*) and *In re Alonso* (Fed. Cir. 2008-1079).

The fact that one could screen for which variants that immunogenic is not the standard for written description. The written description requirement is separate and distinct from the enablement requirement (See also *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 920-23, 69 USPQ2d 1886, 1890-93 (Fed. Cir. 2004) and adequate written description requires more than a mere reference to a potential method for identifying candidate polypeptides. The purpose of the written description requirement is broader than to merely explain how to 'make and use' [the invention] *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1560, 19 USPQ2d 1111, 1114 (Fed. Cir. 1991). Since the

specification only describes only one member of the instant genus of proteins and does not describe the common structure of said genus that correlates with function i.e. immunogenicity, the skilled artisan would conclude that Applicants as of the time of filing were not in possession of the genus of variants to which the claims are drawn.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 8, 14-17 and 23-25 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The scope of independent claims 8 and 17 as written is not clear. Are the claims claiming two different proteins each drawn to:

(1) an isolated variant of an *Erysipelothrix rhusiopathiae* surface protective antigen SpaA protein or

(2) a ΔSpaA protein, which is a shortened form of the SpaA protein in which a portion of the SpaA protein is deleted, which is immunogenic, and expressed in *E. coli* as inclusion bodies and has an amino acid sequence with an amino acid substitution consisting of one or a combination of more than one selected from the group consisting of (1) to (7) as described below:

(1) the 69th amino acid from the N-terminal
encompassing the signal sequence is substituted with glycine;

(2) the 154th amino acid from the N-terminal
encompassing the signal sequence is substituted with glycine;

(3) the 203rd amino acid from the N-terminal
encompassing the signal sequence is substituted with threonine;

(4) the 214th amino acid from the N-terminal
encompassing the signal sequence Is substituted with glutamine;

(5) the 253rd amino acid from the N-terminal
encompassing the signal sequence is substituted with threonine;

(6) the 278th amino acid from the N-terminal
encompassing the signal sequence is substituted with glycine;
and

(7) the 531st amino acid from the N-terminal
encompassing the signal sequence is substituted with glycine.

The recitation of "in which a portion of the SpaA protein is deleted" in claims 8 and 17 renders the claim indefinite because there are two SpaA proteins mentioned in the preceding portions of the claims. Thus, "in which a portion of the SpaA protein is deleted" can be applied to the isolated variant of SpaA protein as set forth above in (1) or applied to a ΔSpaA protein, which is a shortened form of the SpaA protein.

Also, as written in claims 8 and 17, it is not clear as to whether the limitation "which is immunogenic, and expressed in *E. coli* as inclusion bodies and has an amino acid sequence with an amino acid substitution consisting of one or a combination of more than one selected from the group consisting of (1) to (7)…" refers to both the isolated variant of an *Erysipelothrix rhusiopathiae* surface protective antigen SpaA protein and the ΔSpaA protein, which is a shortened form of the SpaA protein.

Applicants are respectfully requested to clarify the claim or possibly rewrite the claim so that the scope of the claim is clear.

The claims recite amino acid substitution(s) at particular positions in SpaA protein. The recitation of said amino acid substitution(s) at particular positions is vague

because there is no sequence of a SpaA protein disclosed in the claims, so that with disclosure of an amino acid sequence, it will be definite as to where in a SpaA protein the amino acid substitution(s) occur.

Claims 15 and 24 recites that the "isolated variant has the sequence as depicted in SEQ ID NO: 2 with deletion at the C-terminal wherein an amino acid substitution is introduced". The claims are indefinite as written because it is not clear whether the amino acid substitution is introduced in the deleted portion at the C-terminal or the amino acid substitution is introduced in the remainder portion after the C-terminal has been deleted.

Furthermore, by "a deletion at the C-terminal" does this mean that the C-terminal amino acid i.e. the last amino acid at the C-terminal is deleted? Applicants can clarify this issue by including the particular amino acid residue(s) of the protein that is substituted. Also, it is not clear as written, whether "wherein an amino acid substitution is introduced" applies to isolated variant which has amino acid sequence as depicted in SEQ ID NO: 2 or only applies to the sequence as depicted in SEQ ID NO: 2 with a deletion at the C-terminal. Applicants are respectfully requested to clarify the claim or possibly rewrite the claim so that the scope of the claim is clear.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 8, 15-17, 24 and 25 are rejected under 35 U.S.C. 102(b) as being anticipated by Fischetti et al. WO 00/47744 August 17, 2000.

The claims are partially drawn to an isolated variant of an *Erysipelothrix rhusiopathiae* surface protective antigen SpaA protein (claim 8); the isolated variant of claim 8 which has an amino acid sequence as depicted in SEQ ID NO: 2 or the sequence as depicted in SEQ ID NO: 2 with a deletion at the C-terminal wherein an amino acid substitution is introduced (claim 15); the isolated variant of claim 8, wherein said SpaA protein is derived from Fujisawa strain (claim 16).

The claims are also partially drawn to a composition comprising as an active ingredient an isolated variant of an *Erysipelothrix rhusiopathiae* surface protective antigen SpaA protein (claim 17); the composition of claim 17, wherein said isolated variant has an amino acid sequence as depicted in SEQ ID NO: 2 or the sequence as depicted in SEQ ID NO: 2 with deletion at the C-terminal wherein an amino acid substitution is introduced (claim 24); the composition of claim 17, wherein said isolated variant is derived from Fujisawa strain (claim 25).

As written in claims 8 and 17, it is not clear as to whether the limitation "which is immunogenic, and expressed in *E. coli* as inclusion bodies and has an amino acid sequence with an amino acid substitution consisting of one or a combination of more than one selected from the group consisting of (1) to (7)…" refers to both the isolated variant of SpaA protein and the ΔSpaA protein, which is a shortened form of the SpaA protein.

For the purposes of this rejection, the claims 8 and 17 are interpreted respectively as being partially drawn to an isolated variant of an *Erysipelothrix rhusiopathiae* surface protective antigen SpaA protein or a composition comprising as an active ingredient an isolated variant of an *Erysipelothrix rhusiopathiae* surface protective antigen SpaA protein.

Fischetti et al teaches an isolated variant of an *Erysipelothrix rhusiopathiae* surface protective antigen SpaA protein called Epa or SpaA.1 which is similar to SpaA. See p. 5.

Said isolated variant has an amino acid sequence as depicted in SEQ ID NO: 2 i.e. 100 % identical to SEQ ID NO: 2. See Appendix A attached.

Fischetti et al also teaches the sequence as depicted in SEQ ID NO: 2 with a deletion at the C terminal i.e. an N-terminal portion of said Epa or SpaA.1 (see p. 6 lines 17-19) and a functional conservative variant of said N-terminal portion (p. 9 lines 27-30) wherein an amino acid substitution is introduced (see p. 10 lines 10-22). Said N-terminal portion as disclosed by Fischetti et al has "an amino acid sequence" as depicted in SEQ ID NO: 2.

Fischetti et al teaches a composition i.e. a vaccine comprising as an active ingredient said isolated variant which has an amino acid sequence as depicted in SEQ ID NO: 2 or said N-terminal portion wherein an amino acid substitution is introduced. See p. 22 lines 21-32.

As to the limitation of being "expressed in *E.coli* as inclusion bodies", this is a process limitation. The instant claims are drawn to the product and not how the instant proteins are expressed or to be used later. "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted).

Status of Claims

13. Claims 8, 14-17 and 23-25 are rejected. Claims 15 and 24 are objected to. Claims 1-7 and 26-45 are withdrawn.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Oluwatosin Ogunbiyi whose telephone number is 571-272-9939. The examiner can generally be reached on M-F 8:30 am - 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Robert Mondesi can be reached at 571-272-0956.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/Oluwatosin Ogunbiyi/

Examiner, Art Unit 1645

/Robert B Mondesi/

Supervisory Patent Examiner, Art Unit 1645